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Seasonal variation of immune hemolytic anemia

İmmün Hemolitik Aneminin Mevsimsel Değişkenliği

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ABSTRACT

Aim: Immune hemolytic anemia is an autoimmune disease that is related to autoantibodies against erythrocytes. Such antibodies appear for a variety of reasons such as hematologic and oncologic malignancies, infections, and connective tissue diseases but in many cases, a true etiologic agent has not been discovered. Many hematologic as well as rheumatologic disorders have seasonal variations but there have not been many studies evaluating the possibility of seasonal variation of immune hemolytic anemia.
Methods: It was investigated whether the patients with immune hemolytic anemia who were diagnosed and followed in the hematology outpatient and inpatient clinic of Suleyman Demirel University from 2002 to 2018 had a significant seasonality. We also evaluated whether there was any seasonality relationship between gender and beginning of the hemolytic attacks.
Results: There was no significant difference when seasons were grouped as spring, summer, autumn and winter, according to gender (p = 0,122). The evaluation of seasons in two groups as autumn-winter and spring-Summer revealed that male patients tended to suffer immune hemolytic anemia in autumn-winter, whereas females, significantly, tend to contract the disease in spring-Summer (p=0,046).
Conclusion: Immune hemolytic anemia had significant seasonality pattern depending on gender. More prospective studies are needed to support these findings in this study.

Keywords: Hemolytic anemia, seasonality, gender

ÖZ

Amaç: İmmün hemolitik anemi, eritrositlerle ilişkili otoantikorlara bağlı otoimmün bir hastalıktır. Bu tür antikorlar, hematolojik ve onkolojik maligniteler, enfeksiyonlar ve bağ dokusu hastalıkları gibi çeşitli nedenlerle ortaya çıkar ancak, bazı durumlarda, etyolojik faktör tespit edilememektedir. Hematolojik ve romatolojik bozuklukların birçoğunun mevsimsel varyasyonları vardır, ancak immün hemolitik aneminin mevsimsel değişim olasılığını değerlendiren çok fazla çalışma yoktur.
Metod: 2002-2018 yılları arasında Süleyman Demirel Üniversitesi hematoloji polikliniğinde ve yatarak tedavi kliniğinde tanı ve takibi yapılan immün hemolitik anemili hastaların anlamlı mevsimselliğe sahip olup olmadığı araştırıldı. Ayrıca, immün hemolitik anemi atağının başlangıcı ile cinsiyetler arasında mevsimsellik ilişkisi olup olmadığı araştırıldı.
Bulgular: Cinsiyete göre mevsimler ilkbahar, yaz, sonbahar ve kış olarak gruplandırıldığında anlamlı fark yoktu (p = 0,122). Mevsimleri sonbahar-kış ve ilkbahar-yaz olarak iki grupta değerlendirdiğimizde, erkek hastaların sonbahar-kış aylarında immün hemolitik anemiye eğilimli olduklarını, kadınların ise ilkbahar-yaz aylarında önemli ölçüde hastalığa yakalanma eğiliminde olduklarını bulduk.
Sonuç: İmmün hemolitik aneminin, cinsiyete bağlı olarak, istatistiksel olarak anlamlı mevsimsellik paterni olduğunu gösterdik. Bu çalışmadaki bulguları desteklemek için daha fazla prospektif çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: Hemolitik anemi, mevsimsellik, cinsiyet.

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INTRODUCTION

Immune hemolytic anemia is an autoimmune disease that progresses with the formation of autoantibodies against erythrocytes. It is a rare disease and its incidence is around one in 100 000 [1]. Depending on the types of antibodies, the disease can be defined as a warm antibody disease, cold antibody disease and paroxysmal cold hemoglobinuria. The most common type is warm antibody (70%) which causes IgG or complement mediated hemolysis at body temperature (37 oC) [2, 3]. Immune hemolytic anemia due to cold antibody is seen around 20% of cases and leads to hemolysis with IgM type autoantibody. This antibody binds to erythrocytes when the body temperature drops in a cold environment and causes hemolysis. While 8% of cases had both types of autoantibodies [4], 2% of cases presented with Donath-Landsteiner type autoantibodies: such antibodies bind to erythrocytes when the body temperature drops in the cold environment, but hemolysis occurs only when the body temperature returns to normal levels. These antibodies, which have historically been observed as a sign of tertiary syphilis, are now emerging after some viral infections [5]. The most common etiology of immune hemolytic anemia is idiopathic, however viral infections, connective tissue diseases, drugs, post-transplantation, hematologic and oncologic malignancies are other known causes [6]. Evaluation of the etiology is of great importance, especially in the choice of treatment; in hemolytic anemia due to malignancies, connective tissue and autoimmune disorders, the treatment of the primary disease that causes hemolysis may stop the hemolytic process, but these non-specific treatments without etiology research may suppress the underlying pathology, leading to serious delays in actual diagnosis and treatment [2, 3, 6]. Corticosteroids in warm antibody positive patients and Rituximab in cold antibody positive patients, are the treatments of choice [2, 3]. Immune hemolytic anemia is a chronic disease in adults; the response rate of first-line treatment is high, but so as the relapse rate and new treatments with different drugs are often needed [6].

The relationship of the seasons in the emergence of hematologic diseases was firstly noticed in clinical observations and later confirmed by various trials. Studies evaluating the relationship between seasons and acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin lymphoma and immune thrombocytopenic purpura showed significant difference in the seasonality of these diseases. We could only find one abstract evaluating the relationship between seasons and immune hemolytic anemia, and a search in Pubmed and other indexes did not reveal any studies from our country. Therefore, our goal was to investigate whether there is any relationship between the emergence of immune hemolytic anemia and the seasons.

MATERIAL and METHOD

This is a retrospective study evaluating patients diagnosed with immune hemolytic anemia who applied to the Hematology Department of the Suleyman Demirel University Medical Faculty Hospital from 2002 to 2018. Permission for the study with number 205 was obtained from Suleyman Demirel University Faculty of Medicine Ethics Committee in 19.06.2019. Patients above 18 years old and who were not pregnant were included in the study. Patients who had been diagnosed and treated prior to 2002 and after 2018, were excluded from the study.

In the definition of etiology for the study, autoimmune hemolytic anemia was related to idiopathic, connective tissue disorders, hematologic malignancies and oncologic malignancies, whereas drug usage was classified separately. Etiology was further re-evaluated as primary and secondary and additional disorders were grouped separately. Patients who had atherosclerotic disease or autoimmune disorders were also analyzed separately. While transfusion independence was accepted as a response criterion for treatment, each different pharmacological agent or splenectomy treatment received was considered as a separate treatment. Treatment groups were organized as steroid treatment on one hand and other treatments on the other. Response to each line of treatment was recorded. Seasons were divided into groups as winter (December, January, and February), spring (March, April, and May), Summer (June, July, and August) and autumn (September, October,

and November). The seasons were then re-grouped as autumn-winter and spring-Summer and further analysis was performed for seasonal variation, while analysis was carried out not only seasonally, but also by months. The demographic properties, the parameters described above and their seasonal variations were then analyzed for any significance.

Statistical analysis was made using SPSS version 22.0. The suitability of variables to normal distribution was examined using the Komogorov-Smirnov/Shapiro-Wilk tests. Descriptive statistics n (%) was presented with mean ± standard deviation and median ± interquartile range. To determine whether the research group was the same in every season, a single group chi-square test was performed. Frequency of immune hemolytic anemia according to seasons was given by using cross tables according to gender, etiology, additional disease and treatment status. Whether there had been a difference in these frequencies between groups was compared using the chi-square, or the Fisher test where the values observed in the cells did not provide chi-square test assumptions. The age variable was compared using the Kruskall-Wallis test between groups, since it was determined that the age continuous variable did not show normal distribution. P <0.05 was considered as statistically significant.

RESULTS

A total of 37 patients with immune hemolytic anemia were evaluated. While 67.6% of the study group were women, 89.2% of them were primary hemolytic anemia, 91.9% received steroid treatment. The average age of the group was 54.3 ± 16.6 years. The demographic and clinical features of the patients are shown in Table 1. To determine whether the ratio of patients with immune hemolytic anemia differ between seasons, a single group chi-square test was performed. There was no statistically significant difference between expected and observed values according to the seasons (Table 2; p = 0.184).

The distribution of the demographic data of the patients such as gender, etiology, additional disease, treatment and age by season was examined (Table 3). When seasonal differences were evaluated according to the gender of patients with immune hemolytic anemia, there was no significant difference between seasons (p = 0,122). The evaluation of seasons in two groups as autumn-winter and spring-Summer revealed that males tended to suffer hemolytic anemia in autumn-winter whereas females significantly tend to contract the disease in spring-Summer (Table 1; p = 0.046). When the seasonal distribution of the patients according to etiology, comorbidities, treatment preferences and age groups was examined, there was no statistically significant difference between them (Table 3). Furthermore, no statistical difference was found when data were evaluated by monthly distribution.

DISCUSSION

In this study, evaluation of the relationship between seasons and attacks of immune hemolytic anemia revealed no significant difference between seasons. When seasons were regrouped as autumn-winter and spring-Summer, it was shown that male patients significantly had more attack in autumn-winter, whereas female patients had significantly more attack in spring-Summer. There were several studies evaluating the seasonality of hematologic disorders. In their study, Karimi and Yarmohammadi found a significant increase of childhood acute lymphoblastic leukemia in the autumn and winter seasons [7]. In another study conducted in patients with adult acute myeloid leukemia, a significant increase in the diagnosis of disease was observed in adult men in December and January [8]. The authors suggested that infections can be associated with this condition. In our study, no relationship could be found between seasons and disease and a subgroup analysis of data evaluated by months failed to find any statistical significance. Borchman et al. evaluated the seasonal pattern of incidence and mortality of Hodgkin Lymphoma and found that incidence of Hodgkin Lymphoma was increased in March. The authors speculated that this might be related to vitamin D status of patients [9]. These retrospective studies yielded conflicting results of seasonality of the hematologic malignancies; therefore large prospective studies are needed to evaluate this subject.

There were also studies showing a possibility of relationship between the incidence of hematologic

Table 1: The demographic properties and seasonal-gender distribution of immune hemolytic anemia

				spring-summer		autumn-winter	
		N	%/ort ±SS	N	%	N	%
Gender	Male	12	32.4%	9	75.0%	3	25.0%
	Female	25	67.6%	10	40.0%	15	60.0%
Etiology	Primary	33	89.2%				
	Secondary	4	10.8%				
Atherosclerotic disease	-	20	54.1%				
	+	17	45.9%				
Autoimmune disorder	-	33	89.2%				
	+	4	10.8%				
Other chronic disorders	-	22	59.5%				
	+	15	40.5%				
Steroid treatment	-	3	8.1%				
	+	34	91.9%				
Secondary treatments	-	32	86.5%				
	+	5	13.5%				
Response to treatment	-	4	10.8%				
	+	33	89.2%				
Age		37	54.3+_16.6				

-: Negative +: Positive

Table 2: Hemolytic anemia attack per month (single group chi-square test)

		Observed value(N)	Expected Value(N)	P
Months	January	4	2.7	0.905
	February	3	2.7	
	March	1	2.7	
	April	2	2.7	
	May	2	2.7	
	June	2	2.7	
	July	4	2.7	
	August	5	2.7	
	September	3	2.7	
	October	2	2.7	
	November	2	2.7	
	December	2	2.7	

disorders other than malignancy and seasons. Raval et al. evaluated 73 patients with thrombotic thrombocytopenic purpura (TTP) and found no seasonal variation in TTP [10]. In contrast to previous study, Park et al. had found that, significantly more TTP attacks occurred in spring [11]. In a study from our country, the incidence of idiopathic thrombocytopenic purpura (ITP) increases significantly in the spring: the authors thought that this was related to pollen exposure in this season [12]. In another study one year later, it was shown that ITP, which lasted less than 3 months, was significantly higher in January and February, but there was no such monthly or seasonal change in chronic ITP [13]. The authors speculated that the peak seen in January and February was related to viral infections. Unlike previous studies, a retrospective trial with 69 181 patients in the United States did not detect any relationship between ITP-related hospitalizations and seasons [14]. These conflicting results showed that more studies are needed to investigate the relationship between seasons and non-malignant hematologic disorders.

We could only find one study about the relationship between autoimmune hemolytic anemia and seasons. Guntupalli et al. retrospectively evaluated 48 416 hospitalizations in United States from 2000

Table 3: The seasonal distribution of demographic and clinic characteristics of patients

		N	%	N	%	N	%	N	%	p
Gender	Male	3	25.0%	6	50.0%	2	16.7%	1	8.3%	0.122
	Female	4	16.0%	6	24.0%	3	12.0%	12	48.0%	
Etiology	Primary	7	21.2%	11	33.3%	4	12.1%	11	33.3%	0.649
	Secondary	0	0%	1	25.0%	1	25.0%	2	50.0%	
Atherosclerotic disease	-	4	20.0%	8	40.0%	2	10.0%	6	30.0%	0.678
	+	3	17.6%	4	23.5%	3	17.6%	7	41.2%	
Autoimmune disorders	-	7	21.2%	10	30.3%	5	15.2%	11	33.3%	0.539
	+	0	0%	2	50.0%	0	0%	2	0%	
Other additional disorders	-	5	22.7%	6	27.3%	3	13.6%	8	36.4%	0.829
	+	2	13.3%	6	40.4%	2	13.3%	5	33.3%	
Steroid treatment	-	1	33.3%	1	33.3%	0	0%	1	33.3%	0.849
	+	6	17.6%	11	32.4%	5	14.7%	12	35.3%	
Secondary treatments	-	6	18.8%	11	34.4%	5	15.6%	10	31.3%	0.556
	+	1	20.0%	1	20.0%	0	0%	3	60.0%	
Response to treatment	-	1	25.0%	2	50.0%	1	25.0%	0	0%	0.470
	+	6	18.2%	10	30.3%	4	12.1%	13	39.4%	
Age	Median±interquartile range		51.0±14.0		41.5±33.0		54.0±14.0		57.0±23.0	0.522

-: Negative +Positive

to 2012 and found a notable increase in winter and autumn, and a significant drop during summer months [15]. In our study, while there was no difference when seasons were grouped separately, a significant increase in frequency of hemolytic attacks was seen in men in autumn-winter and in women in spring-Summer seasons. This could be attributed to several reasons. Men tend to get diverse viral infections more easily compared to women and in autumn and winter, incidences of viral infections are also higher than other seasons, so this could explain the male predominance of hemolytic attacks in autumn-winter [16, 17]. Immune dysregulation, which was triggered by exposure to antigenic stimulus and derived by T helper 1 lymphocytes, was the major pathway for autoimmune disorders. Previous studies have shown that the number of circulating lymphocytes undergoes seasonal changes, reaching a peak in winter months [18]. So, this could also be a link to higher incidences of hemolytic attacks in males during winter period. In spring and autumn, pollen exposure is higher than the other seasons [19] and this led to more antibody production than the other seasons. In fact, some studies have shown that there could be a relationship between allergy and autoimmune disorders [20]. Duarte-García et al. found that arthritis and photosensitivity were more common in summer in women with systemic lupus erythematosus [21]. Hassan et al. also found significant SLE activity in sunny periods [22]. And lastly, Boctor et al. found a significant increase in the activity of lymphocytes in female patients, compared to males in summer periods when stimulated with Phytohemagglutinin and Concanavalin A [18]. So, both pollen stimulus and the increase in activity of lymphocytes, can lead to significant hemolytic attack activity in women. Additional unexplained factors may play a role in seasonal variation of immune hemolytic anemia, however additional prospective studies should be performed to evaluate this subject.

Limitations

Our study had some limitations. It was not a prospective study and the number of patients who participated in this study was not very large: a prospective study with a large number of patients is clearly needed. We could not reach the data regarding the antibody status of the patients. Etiology of warm and cold antibody-induced hemolytic anemia can be different, and it might have been interesting to see whether there was any significant seasonality between cold and warm antibody induced hemolytic attacks. Our study is however unique namely for being the first of its

kind in evaluating the subject in our country. Based on the inconsistent results from previous studies evaluating seasonality of hematologic disorders other than immune hemolytic anemia, repeated studies should be done to evaluate the seasonal variations. Our study highlights the subject for these reasons and can be a steppingstone for future research exploring hemolytic anemia.

Conclusion

In conclusion, male patients had suffered significantly more hemolytic attacks in the fall and winter periods compared to females, whereas females had a higher incidence of hemolysis in the spring and summer seasons. This could be attributable to antigenic stimulus, such as pollen exposure and viral infections or variations in activity of T lymphocytes to antigenic stimulus. Large, prospective studies are needed to explain the etiology of these variations.

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REFERENCES

1. Liebmann HA, Wietz IC. Autoimmune hemolytic anemia. Med Clin N Am 2017;101(2):351–9 doi: 10.1016/j.mcna.2016.09.007.
2. Quist E, Koepsell S. Autoimmune Hemolytic Anemia and Red Blood Cell Autoantibodies. Arch Pathol Lab Med. 2015;139(11):1455-8. doi: 10.5858/arpa.2014-0337-RS.
3. Naik R. Warm autoimmune hemolytic anemia. Hematol Oncol Clin North Am. 2015;29(3):445-53. doi: 10.1016/j.hoc.2015.01.001.
4. Shulman IA, Branch DR, Nelson JM, Thompson JC, Saxena S, Petz LD. Autoimmune hemolytic anemia with both cold and warm autoantibodies. JAMA. 1985;253(12):1746-8. PMID: 3974053.
5. Shanbhag S, Spivak J. Paroxysmal cold hemoglobinuria. Hematol Oncol Clin North Am. 2015;29(3):473-8. doi: 10.1016/j.hoc.2015.01.004.
6. Kalfa TA. Warm antibody autoimmune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2016;2016(1):690-7. doi: 10.1182/asheducation-2016.1.690.
7. Karimi M, Yarmohammadi H. Seasonal variations in the onset of childhood leukemia/lymphoma: April 1996 to March 2000, Shiraz, Iran. Hematol Oncol. 2003;21(2):51-5. doi: 10.1002/hon.702.
8. Calip GS, McDougall JA, Wheldon MC, Li CI, De Roos AJ. Evaluation of seasonality in the diagnosis of acute myeloid leukaemia among adults in the United States, 1992-2008. Br J Haematol. 2013;160(3):343-50. doi: 10.1111/bjh.12137.
9. Borchmann S, Müller H, Engert A. Hodgkin Lymphoma has a seasonal pattern of incidence and mortality that depends on latitude. Sci Rep. 2017;7(1):14903. doi: 10.1038/s41598-017-14805-y.
10. Raval JS, Harm SK, Rollins-Raval MA, Kiss JE. Seasonal distribution of severe ADAMTS13 deficient idiopathic thrombotic thrombocytopenic purpura. J Clin Apher. 2014;29(2):113-9. doi: 10.1002/jca.21300.
11. Park YA, Poisson JL, McBee MT, Afenyi-Annan A. Seasonal association of thrombotic thrombocytopenic purpura. Transfusion. 2012;52(7):1530-4. doi: 10.1111/j.1537-2995.2011.03481.x.
12. Tombak A, Boztepe B, Tiftik N, Cömert M, Salim O, Aydın K, et al. Seasonal Association of Immune Thrombocytopenia in Adults. Balkan Med J. 2015;32(4):347-51. doi: 10.5152/balkanmedj.2015.151223.
13. Moulis G, Guénin S, Limal N, Michel M, Bierling P, Godeau B, et al. Seasonal variations of incident primary immune thrombocytopenia in adults: An ecological study. Eur J Intern Med. 2017;37: e26-e28. doi: 10.1016/j.ejim.2016.09.025.
14. Giri S, Pathak R, Aryal MR, Karmacharya P, Bhatt VR, Martin MG. Seasonal variation of immune thrombocytopenic purpura related hospitalizations among adults in the USA: analysis of the nationwide inpatient sample database. Ther Adv Hematol. 2015;6(4):217-8. doi: 10.1177/2040620715582146.
15. Guntupalli S, Patel D, Soni RGK, Devarashetty S, Mansour RP. Seasonal Variation in Autoimmune Hemolytic Anemia: A National Database Analysis. Blood 2018;132 (Suppl. 1):4883. doi: 10.1182/blood-2018-99-113882.
16. Vom Steeg LG, Klein SL. SeXX Matters in Infectious Disease Pathogenesis. PLoS Pathog. 2016;12(2): e1005374. doi: 10.1371/journal.ppat.1005374.
17. Morgan R, Klein SL. The intersection of sex and gender in the treatment of influenza. Curr Opin Virol. 2019;35:35-41. doi: 10.1016/j.coviro.2019.02.009.
18. Boctor FN, Charmy RA, Cooper EL. Seasonal differences in the rhythmicity of human male and female lymphocyte blastogenic responses. Immunol Invest. 1989;18(6):775-84. doi: 10.3109/08820138909030598.
19. Rodríguez-de la Cruz D, Sánchez-Reyes E, Dávila-González I, Lorente-Toledano F, Sánchez-Sánchez J. Airborne pollen calendar of Salamanca, Spain, 2000-2007. Allergol Immunopathol (Madr). 2010;38(6):307-12. doi: 10.1016/j.aller.2010.04.001.
20. Pedullá M, Fierro V, Papacciuolo V, Alfano R, Ruocco E. Atopy as a risk factor for thyroid autoimmunity in children affected with atopic dermatitis. J Eur Acad Dermatol Venereol. 2014;28(8):1057-60. doi: 10.1111/jdv.12281.
21. Duarte-García A, Fang H, To CH, Magder LS, Petri M. Seasonal variation in the activity of systemic lupus erythematosus. J Rheumatol. 2012;39(7):1392-8. doi: 10.3899/jrheum.111196.
22. Hasan T, Pertovaara M, Yli-Kerttula U, Luukkaala T, Korpela M. Seasonal variation of disease activity of systemic lupus erythematosus in Finland: a 1 year follow up study. Ann Rheum Dis. 2004;63(11):1498-500. doi: 10.1136/ard.2003.012740.

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